March 26, 1992. The interview was helpful in clarifying the rejections of the claims.

Claims 1, 2, 5-7, 10 and 13-15 presently remain under consideration in the application. Applicants have reviewed the rejections of the claims, but traverse all such rejections for the reasons set forth below.

I. Rejections Under 35 U.S.C. §112

Claims 1, 2, 5-7, 10 and 13-15 stand rejected as being non-enabled by the written description or for indefiniteness. With regard to claim 1, the Examiner states the word "agent" is vague and unclear since the nature of the "agent" is indeterminate. Applicants have amended claim 1 to clarify that such agents specifically suppress the activity of TGF-ß to distinguish them from non-specific agents such as actinomycin D, for example. In addition, the term "agent" is well defined in the specification, for example, on page 8, line 33, through page 9, line 6.

The Examiner further alleges that Applicants have only shown an antibody that inhibits TGF-ß activity. Applicants note that Example I (page 13, lines 25-27) and Example VIII (pages 24-25) specifically describe studies in which PDGF and Arg-Gly-Asp containing peptides were effective in addition to anti-TGF-ß antibodies. Applicants accordingly contend the claims should not be limited merely to anti-TGF-ß antibodies.

Next, the Examiner alleges the phrase "extracellular matrix" in claim 1 is vague and unclear since it includes more than the proteins decorin and biglycan investigated by Applicants. The Examiner also alleges on page 4, lines 14-19, of

the Office Action, that this phrase is vague and unclear in claims 6 and 13 as well. Applicants note that claim 13 does not contain the phrase "extracellular matrix," and therefore should not be rejected.

With regard to claims 1 and 6, Applicants contend that more proteins than decorin and biglycan were studied. The results of the study shown in Figure 17(b) and reported in Example VII clearly show that the treated tissues contained less extracellular matrix compared with untreated tissues. The histological methods used to obtain the micrographs shown in Figure 17 were the same methods used to determine the percentage of glomerulus occupied by mesangial matrix in Figure 7. As discussed in the paragraph bridging pages 17-18 relating to Figure 7, the method involved scoring the entire extracellular matrix since the staining procedure that was used is non-specific for extracellular matrix proteins and therefore does not identify or distinguish individual components. Since fibronectin is known to be a major component of the extracellular matrix, one skilled in the art would readily know that Figure 17(b) relates to the entire extracellular matrix and not solely to individual proteoglycans.

Applicants' published paper (Okuda et al., J. Clin. Invest. 86:453-462 (1990)), which relates to the present application, provides further evidence that production of fibronectin in the extracellular matrix is also affected by inhibiting the activity of TGF-ß. Although these results are clearly shown in Figure 17(b), the paper provides additional evidence by using a stain specific for fibronectin. A copy of the publication is attached as Attachment A for the Examiner's convenience.

Moreover, Applicants submit that no evidence has been presented to refute the statements in the specification that by inhibiting the activity of TGF-ß, the deleterious accumulation of extracellular matrix will be suppressed. The law is clear the specification is presumed to be enabling absent "a reason to doubt the objective truth of the statements contained" in the disclosure. In re Marzocchi, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971); see also Ex parte Gould, 231 U.S.P.Q. 943, 945 (PTO Bd. App. & Int. 1986).

The Examiner next alleges the phrase "suppresses the extracellular matrix producing activity" is vague and unclear since the mechanism by which this suppression is accomplished is indeterminate and many are known in the art. Applicants contend that the law does not require an applicant to know the mechanism by which an invention works. See Cross v. Iizuka, 224 U.S.P.Q. 739, 741 n.3 (Fed. Cir. 1985)("it is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests"). Applicants have provided sufficient guidance in the specification to enable one skilled in the art to test for agents that have an inhibitory effect on the activity of TGF-ß. Thus, Applicants contend that claims 1 and 6 need not state the exact mechanism by which their invention works.

The Examiner further requires claims 1 and 6 be amended to in vitro usage. As support, the Examiner cites a dictionary definition for the term "tissue" as an aggregate of cells and then alleges that the specification only describes cells grown in petri dishes. Applicants note, however, the specification provides the results of an in vivo study in Example VII.

The Examiner next alleges that it is not apparent that all antibodies to TGF-ß would be effective and therefore requires claims 2 and 7 be limited to the actual antibody used. Applicants, however, contend that these claims do not encompass all antibodies against TGF-ß, but rather only those that suppress the extracellular matrix producing activity of TGF-ß. As discussed above, the specification provides clear guidance for identifying antibodies that have the ability to suppress such activity. Consequently, the claims are clearly enabled by the specification.

Claim 5 is rejected as not being limited to glomerulonephritis. According to the Examiner, the specification fails to show that the claimed methods would work in treating other diseases, such as ARDS and cirrhosis of the liver. As noted above, the law is clear that the specification is presumed to be enabling absent "a reason to doubt the objective truth of the statements contained" in the disclosure. As stated in the specification on page 1, lines 15-23, for example, ARDS and cirrhosis of the liver also involve the inappropriate accumulation of extracellular matrix in these tissues. No evidence has been presented to doubt the truth of the statements made and claimed in the present application or that other contributing reasons may account for the accumulation of extracellular matrix in these diseases.

Regarding claims 6 and 13, the Examiner alleges Applicants have not shown inhibition of "accumulation" of the extracellular matrix, since only synthesis has been shown to be inhibited, but not degradation, and accumulation is dependent on both synthesis and degradation. Applicants first note that claim 13 does not contain the term "accumulation." With regard

to claim 6, Applicants contend that by decreasing the synthesis of extracellular matrix, the overall accumulation of extracellular matrix is decreased as evidenced by Example VII on page 24. This Example provides evidence that anti-TGF-ß treated nephritic rats "contain less" extracellular matrix than non-treated nephritic control rats. Thus, the treated rats clearly accumulated less matrix than the non-treated control rats, which provides clear support for claim 6.

With regard to the rejection of claims 10 and 13, the Examiner states that the claims must be limited to kidney tissues or cells since it is not apparent to the Examiner that the claimed methods would be effective in other tissues. As discussed above, no evidence has been provided to question the truth of the statements made in the specification to support these claims. As such, Applicants contend that the specification must be presumed as accurate. Furthermore, methods of treating pathologies involving various tissues in which the activity of TGF-ß is inhibited are described and claimed in the related applications.

Next, the Examiner points out that the data in Figure 1 reports 8 lanes but only describes 7 lanes. Although the specification does not report which of lanes 5 or 6 relates to 25 ng/ml of TGF-ß, the overall description does provide evidence of the extracellular production of PGI and PGII. The omitted value relates to lane 5, which is 7.5 ng/ml, although this information is not necessary to show the extracellular production of these proteins. The remaining values correspond to the other lanes, which are identified in the brief description of the drawings.

Finally, the specification is objected to under 35

U.S.C. § 112, first paragraph, as failing to provide an adequate written description and failing to enable the claimed invention. Claims 1, 2, 5-7, 10 and 13-15 are correspondingly rejected for the same reasons.

Applicants note that the basis for the rejection is the same as for the rejection of claims 2 and 7 above. Therefore, Applicants' discussion with regard to this rejection is also applicable to the objection to the specification. Specifically, Applicants contend that the claims do not encompass all antibodies against TGF-ß, but rather only those that suppress the extracellular matrix producing activity of TGF-ß. As discussed above, the specification provides clear guidance for identifying antibodies that have the ability to suppress such activity. Consequently, the claims are clearly enabled by the specification.

II. Prior Art Rejections

Claims 1, 6, 10 and 13-15 are rejected under 35 U.S.C. § 102(b) as being anticipated by Bassols et al. As acknowledged by the Examiner in the Interview Summary Record, Bassols et al. fail to disclose treating pathologies. In addition, the Examiner acknowledges that Bassols et al. utilize a general inhibitor. Applicants accordingly request the withdrawal of this rejection.

Next, claims 1, 2, 5-7, 10 and 13-15 are rejected under 35 U.S.C. § 103 as being unpatentable over Flanders et al. in view of Harper et al. Again during the interview, the Examiner acknowledged Flanders et al. failed to disclose treatment of pathologies as evidenced in the Interview Summary Record.

Furthermore, Flanders et al. were concerned with the activity of TGF-ß on the normal production of collagen by cultured cells. Flanders et al. provide no teaching or suggestion that TGF-ß can cause a deleterious accumulation of extracellular matrix components, particularly in tissues, which leads to various pathologies. Flanders et al. were primarily interested in the active sites of TGF-ß. Accordingly, there was no appreciation by Flanders et al. that TGF-ß has a dark side, i.e., its activity can be deleterious. Harper et al. merely disclose culture of mesingial cells obtained from the glomerulus and therefore does not provide the teaching lacking in Flanders et al. Accordingly, the cited references do not obviate the claims.

III. Related Applications

TITLE	SERIAL NO.	FILING DATE
SUPPRESSION OF CELL PROLIFERATION BY DECORIN (abandoned)	212,702	6/28/88
SUPPRESSION OF CELL PROLIFERATION BY DECORIN	645,339	1/22/91
INHIBITORS OF CELL REGULATORY FACTORS	467,888	1/22/90
DECORIN FRAGMENTS AND METHODS OF INHIBITING CELL REGULATORY FACTORS	865,652	4/3/92
INHIBITORS OF CELL REGULATORY FACTORS AND METHODS FOR PREVENTING OR REDUCING SCARRING	792,192	11/14/91
INHIBITORS OF CELL REGULATORY FACTORS AND METHODS FOR PREVENTING OR REDUCING SCARRING		5/13/92

INHIBITING TRANSFORMING GROWTH FACTOR β TO PREVENT ACCUMULATION OF EXTRACELLULAR MATRIX (abandoned)	415,081	9/29/89
INHIBITING TRANSFORMING GROWTH FACTOR β TO PREVENT ACCUMULATION OF EXTRACELLULAR MATRIX	803,285	12/4/91
METHODS FOR TREATING VASCULAR DISORDERS BY INHIBITING THE ENDOTHELIN STIMULATORY ACTIVITY OF TGFβ	872,676	4/23/92
MEANS FOR DETERMINING THE EFFECTIVENESS OF TREATMENT OF PATHOLOGIES CHARACTERIZED BY UNDESIRABLY HIGH LEVELS OF TGF-β	786,108	10/30/91

CONCLUSION

In light of the above amendment and remarks, Applicants respectfully request the withdrawal of all rejections and solicit an allowance of the pending claims. The Examiner is invited to call the undersigned attorney if there are any remaining issues.

Respectfully submitted,

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